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Advances in Drug Delivery Systems and Applications in Neurosurgery

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With 5 Figures

Contents

The principle of direct administration of repeated doses of drugs either at or close to their site of action in the central nervous system is based on:

– the identification of specific receptors and neuro-active endogenous peptides which has considerably advanced our understanding of the functioning of the central nervous system. The notion of chemical transmission of information in specific pathways now underlies the early electrical model of Galvani.

– better understanding of the pharmacological action of endogenous and exogenous ligands, which was led to the development of specific and highly active drugs. Such drugs are now employed routinely in the treatment of chronic conditions such as intractable pain or spasticity. In the near future, it may also be possible to treat other neurological diseases by manipulation of the specific neuromediators or neuromodulators involved.

– the fact that high doses of drug are often required via the systemic route, giving rise to adverse reactions in other parts of the organism before the active agent reaches the target organ. Many drugs do not readily cross the blood-brain barrier, and are degraded in the periphery either in the digestive tract, liver or kidneys. This means that the therapeutic ratio is

low for many drugs. Moreover, distribution in the central nervous system itself is not localized to the site of action (spinal cord for example) which can give rise to supra-spinal side effects.

– advances in technology which have stimulated development of implantable systems enabling local or regional administration of many drugs employed in endocrinology, oncology and neurology.

In neurology, treatment of chronic cancer pain using an implanted system for the intrathecal and intraventricular injection of morphine was first described in 1978. This technique is now in routine use. Over the past 6 years, severe spasticity of central origin has also been treated effectively by intrathecal administration of Baclofen.

We will discuss these two applications (pain and spasticity) which are now a routine part of conservative neurosurgery. We will also mention other indications for "pharmacological neurosurgery" which are currently being tested for effectiveness and safety.

1. Implantable Drug Delivery Systems

The main objectives of drug delivery systems (DDS) are to:

a) provide a non-invasive access to the various compartments of the central nervous system (epidural space, lumbar sub-arachnoid space, cisterns, ventricles, parenchyma, etc). or vascular system,

b) enable single or repeated administration of drugs or contrast media,

c) obtain samples of CSF or blood,

d) prevent leakage of active principle to other organs,

e) employ drugs which are not degraded in contact with the generally inert biocompatible materials used in the construction of the delivery systems,

f) enable treatment on a out-patient basis without risk to the patient.

DDS are implanted subcutaneously, and are connected to flexible catheters whose distal end is placed in the zone or site of action. Various systems from single access ports to micropumps are now available for administration of repeated bolus doses, or continuous or programmable infusions.

1.1 Access Ports

These are small volume rigid chambers placed in contact with the compartment to be infused. They are designed to replace lumbar or intraventricular puncture or intravascular injection by a simple subcutaneous injection. The first systems which were used for intra-ventricular injections consisted of a dome-shaped silicone capsule derived from an Ommaya reservoir. They were then modified by moving the catheter junction to the

periphery. The Unidose reservoir developed by Cordis* is one of the most widely used. It is available in two sizes (1 and 2 ml). It has a stainless steel base-plate which prevents the injection needle passing right through it. However, its dome shape and its thin wall means that it is not self-sealing, and it can only be used a few times, even with fine needles (25 G), before it starts to leak. It is thus not used for repeated chronic administration.

Pharmacia have developed improved access ports under the trade name Port-A-Cath®. They are constructed of stainless steel or titanium closed by a membrane or self-sealing compressed silicone stopper (septum). This septum has a diameter of 10 mm with a surface area around 1 cm^2 and a thickness of 5 to 6 mm. The depth of the chamber under the membrane is between 5 and 8 mm giving a total capacity of 0.5 ml. Over 1000 punctures and injections ats can be made without leakage using a 22 G needle with a Huber type point.

The access port is joined by a safety connector and an anti-kinking system to the catheter whose diameter depends on the actual site of infusion. The Port-A-Cath® system is now widely used in oncology. Various manufacturers now produce similar systems using other biocompatible materials such as stainless steel, polysulfone, reinforced silicone, etc, and more than 20 different models are now available. Examples are the Life-Port®, Infuse-Port®, Polysit®.

The MPAP® system developed by Cordis is of interest as it is equipped with a 7 to 8 mm thick septum with a larger surface area (2.7 cm^2) than

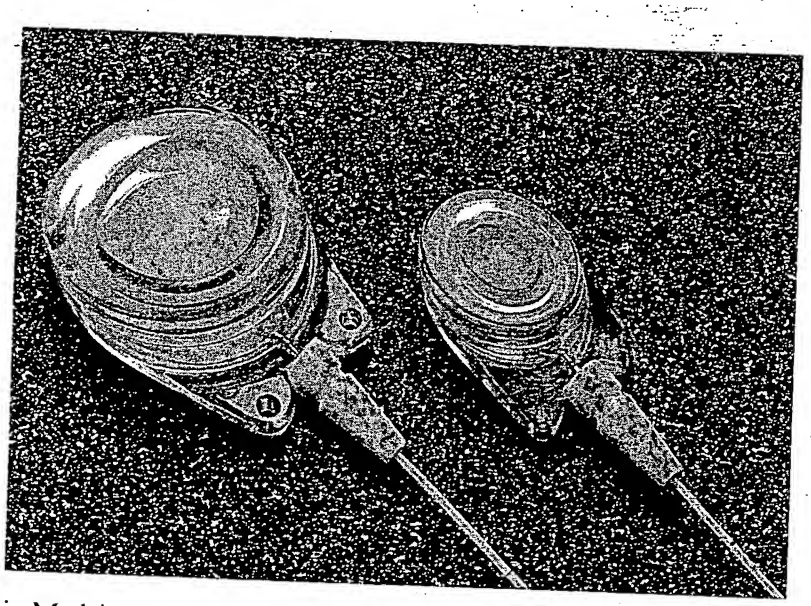

Fig. 1. Cordis Multipurpose Access Port (MPAP)^{tm} and Miniport^{tm} for intrathecal or vascular access

* Cordis Biot Operation, Route des Dolines, Sophia-Antipolis, 06560 Valbonne, France.

the other systems. It is thus easily located under the skin, and can be implanted at an oblique angle to facilitate insertion of indwelling needles for infusion via a portable miniature pump. A miniature version, the Miniport®, with an oblique silicone septum (0.6 cm^2, 6 mm thick) with a 5 to 8 mm deep reservoir is also available. It is employed for intra-arterial administration of drugs used in chemotherapy, and also for intrathecal administration in children as well as adults (Fig. 1).

These systems have the advantage of ease of use and low cost, although the need for repeated injections (daily or even several times a day) into the reservoir restricts the patients mobility, and increases the risk of infection.

1.2 Implantable Pumps

These DDS have reservoirs of varying capacities (generally 12–50 ml) which can be refilled by injection through a self-sealing septum. The freedom of movement of the patient will clearly be influenced by size of the reservoir. The safety and reliability depend in the accuracy and adaptability of the infusion rate (pulsatile or continuous). The different systems can be classified in terms of their programmability, from simple pulsatile pumps to fully programmable, remote-controlled electric pumps.

1.2.1 Pulsatile Pumps

These are purely mechanical hand-operated systems. The Secor® pump produced by Cordis consists of three one-way valves in series which delivers constant volume boluses (0.1 ml ± 10%) (Fig. 2). The dosage is adjusted by varying the number of boluses and/or the concentration of the active principle.

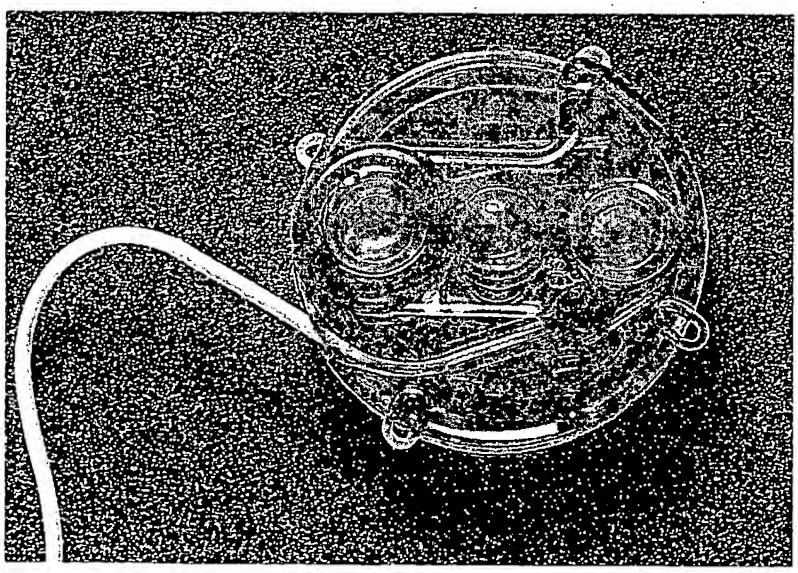

Fig. 2. Cordis Secor^{tm} implantable multidose reservoir

The body of the pump is made of polysulfone (6 cm diam, 1.4 cm deep) and it only weights 45 grams. The useable capacity of the flexible Teflon reservoir attached to the bottom of the unit is 12 to 15 ml.On the first generation of Secor pumps, the two push buttons could not be located easily under the skin. The pump was primed by pressing one button and drug was injected by pressing the other one. The two buttons on the second generation now protrude slightly more, and they incorporate a tactile feedback with a click so that the operator knows that the pump has been operated effectively, and the dose administered.

Although the relative inaccuracy of the Secor pump restricts its application especially for administration of drugs such as Baclofen, its safety and low cost make it particularly suitable for intrathecal administration of opiates in the treatment of intractable cancer pain.

1.2.2 Continuous Flow Pumps

An example is the Infusaid* (model 400) first produced in 1969. The drug solution is forced through the system by a gas (Freon) contained in an external chamber connected to the reservoir containing the drug via flexible bellows made of titanium. At a given temperature, the liquid phase of Freon is in equilibrium with the gas phase and exerts a constant pressure (450 mmHg at 37 °C) thus expelling the drug solution progressively through a regulator valve and bacterial filter (0.22 microns) into the catheter. Re-

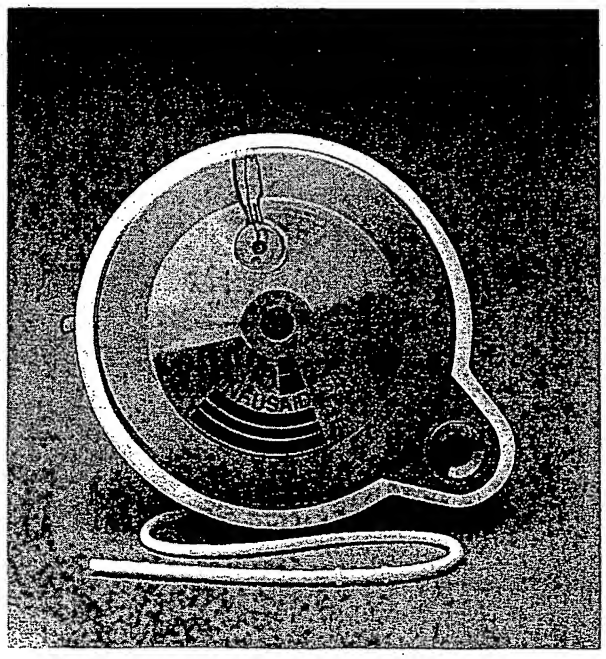

Fig. 3. Infusaid Model 400 continuous flow pump

* Infusaid Inc., 1400 Providence Highway, Norwood, MA 02062, U.S.A.

filling the pump expands the bellows and compresses the propellant gas to a liquid, thereby reactivating the pump.

Inert materials such as titanium, polypropylene, stainless steel, silicone and Teflon are used in the parts of the pump that come in contact with the drug. It has an empty weight of 208 grams with a reservoir capacity of 47 ml, and is the largest currently available. Model 400 (Fig. 3) is also equipped with a side-port enabling administration of more than one drug and verification of the permeability of the catheter. The flow rates of the pumps are factory-set to between 1.0 and 6.0 ml/24 h, and this flow rate cannot be altered after implantation. The only way of altering the dose is by changing the drug concentration in the reservoir. A further disadvantage is that the flow rate depends of the temperature of the patient and the atmospheric pressure. Furthermore, in emergency, the infusion can only be stopped by draining the reservoir. These disadvantages restrict the use of these DDS in neurosurgery when powerful centrally acting drugs are employed, especially if there are no antagonists available, as is the case for Baclofen. On the other hand, these pumps are well suited for intrathecal or intravenous infusion of the relatively large amounts of drugs used in chemotherapy where accurate dosage is not usually required. The new generation of continuous-flow Infusaid pumps are now fitted with flow regulators.

In 1989, Therex* introduced an implantable constant-flow pump with 30 ml capacity employing the same principle as the Infusaid 400 system. There is a yet insufficient experience with this system to come to any firm conclusions, but it is likely to have the same advantages and disadvantages of the Infusaid 400 system.

1.2.3 Programmable Pumps

These are generally electromechanical pumps of the peristaltic type powered by a lithium battery. Their built-in electronics can be remotely controlled from an external programming unit. The most sophisticated and most widely employed in neurosurgery is the Synchromed system manufactured by Medtronic**. The titanium and silicone unit (70 mm diameter, 27.5 mm deep) has an empty weight of 185 grams (Fig. 4) and a useable capacity of 18.0 ml with a 2.4 ml dead space. Energy is provided by a lithium thionyl chloride battery with an average life of 3 years at a flow rate of 1.5 ml/24 h.

The infusion parameters can be remotely controlled, and the flow rate can be adjusted over a range of 0.004 ml/h to 0.9 ml/h. The accuracy of

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* Therex Corp., 1600 Providence Highway, Walpole, MA 02081, U.S.A.

** Medtronic Inc., 7000 Central Av. NE, Minneapolis, MN 55432, U.S.A.

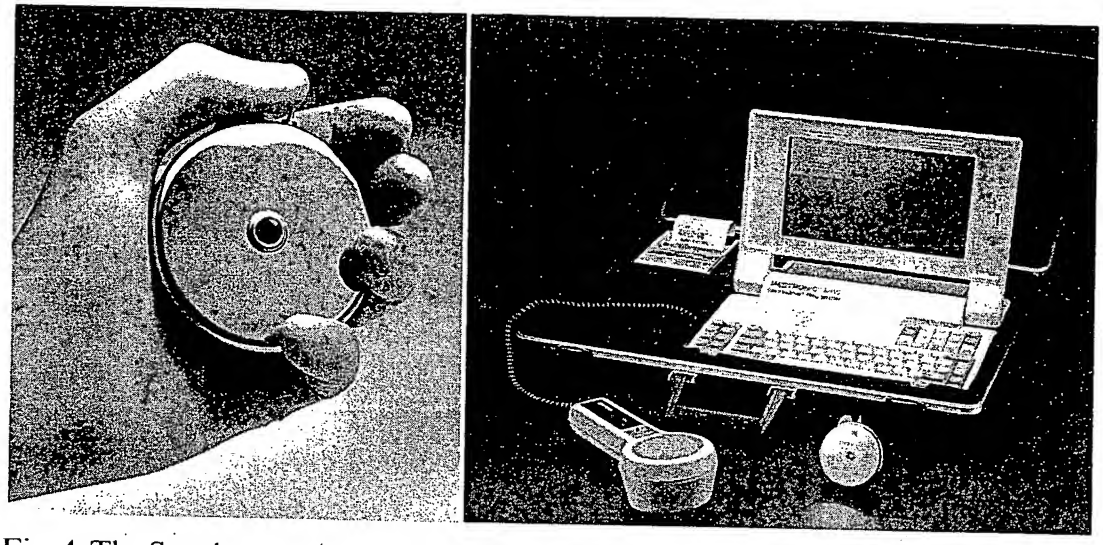

Fig. 4. The Synchromed[tm] infusion system from Medtronic: implantable drug pump and desk-top programmer

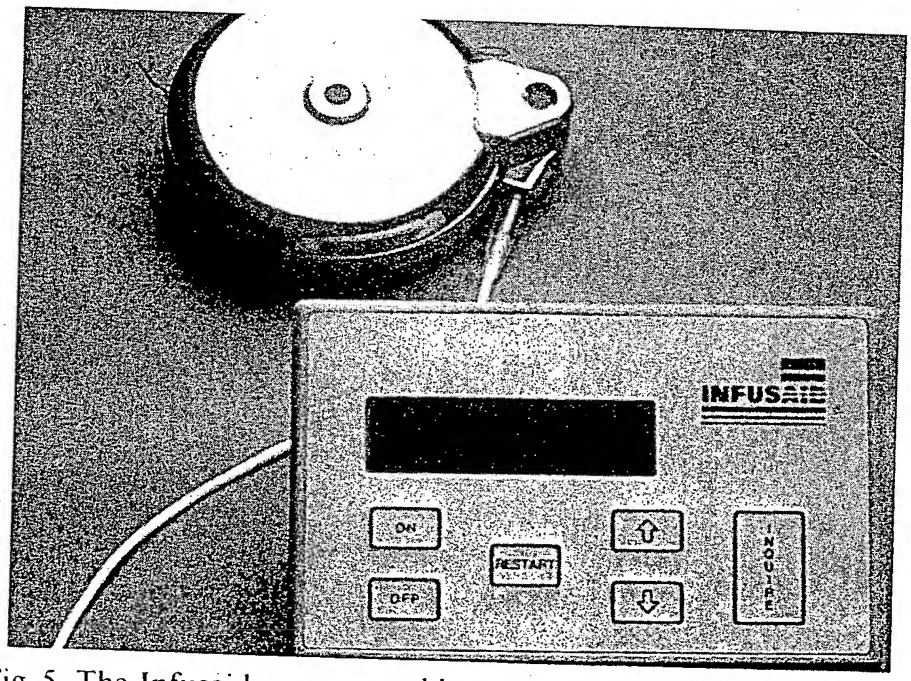

Fig. 5. The Infusaid programmable pump and portable programmer

the flow rate at the tip of the catheter is ± 15% over a temperature range of 35 °C to 42 °C. The infusion can be programmed in various modes: continuous hourly infusion, repeated bolus infusion with a specified delay, multistep dose over a programmed interval, or single bolus infusion. Although the rate of infusion can be programmed, the only way of stopping the infusion is via the remote-control module. This means that the patient either has to go back to the hospital where the device was implanted or

go to a hospital equipped with the relevant programming unit. This is a major disadvantage, and it is a pity that there is no provision for the patient himself to switch the pump on or off. We have instructed all our patients equipped with this system, especially those that live far from the hospital or that travel widely, on how to drain and rinse out the reservoir with sterile saline in an emergency. Even after drainage, the pump will continue to infuse drug contained in the dead space, and patients must be aware that drainage of the reservoir will not stop infusion immediately. In addition, even when the pump is programmed to stop, the motor idles and infusion will still continue, albeit at a low flow rate (0.00018 ml/h). In practice this does not present any risk to the patient.

Infusaid have recently developed their own implantable programmable pump, the model 1000 (Fig. 5). It is quite large (90.2 mm diameter, 22.5–26.7 mm deep, empty weight 272 g) with a useable capacity of 22 ml. It is also equipped with a side-port. It is derived from the model 400 as it is also powered by the expansion of an inert gas (Freon) through flexible metal bellows. However, the output flow rate is regulated by a system of battery-powered, electronically controlled valves. Flow rates can be adjusted between 0.001 and 0.5 ml/h as periodic flow, multiple flow rates or as a single bolus infusion. The programming unit is miniaturized and portable, which increases patient comfort and safety. Unfortunately, it is rather costly, and this must be taken into account in the overall context of health care expenditure.

2. Implantation Techniques

Subcutaneous implantation can usually be carried out under local or neuroleptic anaesthesia. However, implantation of a spinal catheter can be carried out by laminectomy, and in spastic patients, it is generally preferable to perform the operation under general anaesthesia. The surgical technique is straightforward and will not be discussed in detail here. It has been described in numerous publications[60, 63, 64, 65, 68, 70, 71]. Nevertheless, it should not be regarded as a minor operation. Strict asepsis must be maintained at all times, and the positioning and permeability of the catheter must be checked carefully. A convenient point of connection to the access port or pump must be made available, and there must be a perfect seal between the system and the infusion catheter. The numerous complications (displacement of the implant, kinking or stenosis of catheter, fistula or accumulation of CSF, disconnection or subcutaneous leakage of drug, sepsis, meningitis, ets.) which may arise, can be avoided by the use of high quality materials and a rigorous technique. It is thus particularly important to check every step of the procedure to avoid technical complications which are not intrinsic to either the method or its application.

2.1 Catheter Placement

The technique depends of the site: spinal, intraventricular or intraarterial. The catheter is passed under local anesthetics or neuroleptanalgesia and under radioscopic control to determine its exact location.

A 14 G or a 16 G Touhy needle permits to place the intra-spinal catheter into the subarachnoid space. We use a percutaneous lumbar lateromedian approach so that the puncture pathway is as oblique as possible in order to avoid catheter kinkage during interlaminar penetration of the vertebral canal. It is extremely important that the connection is leak-free to prevent CSF fistulas and subcutaneous drug leakage.

The intraventricular implantation is done via a classical ventricular puncture. The distal tip of the catheter is either placed in the frontal horn of the right lateral ventricle close to the foramen of Monro or in the third ventricle.

2.2 Implantation of a Drug Administration System

Regardless of whether you are using an access port or a pump make sure that the pocket is situated 2–3 cm beyond the incision, not directly on top of it, but yet close enough fo facilitate fixation and to control the catheter connection. The subcutaneous surface must be thick enough to prevent skin necrosis especially with large-size pumps; but on the other hand, the system must not be implanted too deeply in order to facilitate transcutaneous palpation (filling, tactile feed-back, ...). Each system has its own particularities:

The access port. The entire system (catheter-connector-reservoir) should be as straight as possible in order to avoid kinks and assure optimal permeability. Before fixing the access port in the subcutaneous pocket the permeability is tested. For reservoir puncture, a 25 G needle will preserve the self-sealing properties of the septum. During chronic drug administration, the permeability of the system is controlled by observing a CSF reflux, by taking CSF samples for bacteriological analysis and/or by opaque solution injection, if necessary. Drug injection must be done slowly; once the needle is removed, and, if possible the septum is pushed down so that the bolus is progressively ejected into the subarachnoid space. The reservoir can be rinsed with an additional 1–2 ml bolus of CSF which has been drawn prior to injection of the drug.

The mechanical multidose pumps (Secor I and II, Cordis). Its fairly large size requires implantation on the lower latero-thoracic level for intraspinal administration, while the subclavicular level is more suitable for intraventricular administration. Before connecting the reservoir, we must purge it of all air bubbles by filling it with a sterile saline solution. The pump must per-operatively calibrated to check the bolus volume (0.1 ml + 10%) and filled with the drug solution.

The programmable drug administration device (Synchromed, Medtronic). Prior to implantation, remove all water in the reservoir and fill it up with 20 cc of drug solution in a sterile manner. Using the programmer under sterile conditions, we can then proceed with the examination and programmation. We must feed in data concerning the patient, the metrology and the nature of the drug to be administered (baclofen, morphine, antimitotics, saline solution, etc). The limits of the "empty reservoir" alarm must then be set. In practive, according to the pumps specific flow rate, we must program the quantity of drug that can be consumed before the audible alarm rings. At this point, the pump is submerged in 37 °C water to check if all the bubbles have been completely evacuated. Considering the pumps large size, it is preferable to make the subcutaneous pocket in the flank of in the para-umbilical abdominal area. The pump is now ready to be programmed. The programmer includes a computer-type console television screen, keyboard and transmission head. Programming is simplified by the fact that the software guides the manipulator, eliminating any chance of error.

3. Current Clinical Applications

Over the last decade, the use of implantable drug delivery systems has seen considerable development for the treatment of intractable pain and severe spasticity. There are now sufficient clinical data to determine their place in the treatment of these conditions.

3.1 Intrathecal Spinal and/or Intra-cerebro-ventricular Morphine in Intractable Cancer Pain

This was the first application of DDS in the central nervous system. It is based on fundamental understanding in neurochemistry and considerable experimental evidence.

3.1.1 Neurobiological Basis

A series of recent reports concerning the direct action of morphine on both the spinal cord[19, 32] and brain[1, 49, 73, 75, 116, 119], along with the discovery[42, 52, 98, 111] and localization[2, 3] of specific opiate binding sites and endogenous ligands has spurred development of new therapies for chronic pain, such as intrathecal morphinotherapy. This is the direct administration of opiates, especially morphine, into the perispinal and intraventricular cerebro-spinal fluid. Animal studies have shown that administration of morphine directly to the cerebrospinal fluid produces an intense and durable analgesia which is localized, dose-dependent, stereospecific and naloxone-reversible[119, 120]. These studies paved the way for the clinical use of intrathecal morphine[44,

[46, 80, 88, 90, 117]. It is mainly indicated for intractable cancer pain in the lower half of the body. With spinal administration, the analgesic effect has a limited distribution, and there is less risk of central respiratory depression than when treatment is given for pain of diffuse or cervico-cephalic origin. The existence of intracerebral opiate receptors[3, 98, 113], especially around the walls of the third and fourth ventricles, and the analgesic action of intracerebral micro-injections of morphine[1, 30, 116], has encouraged various workers to try direct intraventricular administration of morphine in humans[10, 69, 72, 74, 76, 86, 101, 115]. The efficiency, specificity and risks of spinal and intraventricular administration of opiates have now been evaluated in a number of clinical studies[64, 68, 72, 86].

3.1.2 Selection Criteria

Indications for this route of administration of morphine are based on clinical criteria backed up by results of intrathecal tests. Inclusion criteria are the existence of pain:

a) of a chronic nature due to inoperable, invasive and generally terminal cancer,

b) resulting from excess nocioceptive stimulation,

c) resistant to standard medical treatment such as administration of progressive doses of analgesics according to WHO guidelines. These patients must be either inadequately relieved and/or have adverse reactions to prolonged administration of morphine or its derivatives via the systemic, subcutaneous or oral routes (using oral solutions such as Brompton cocktail or slow-release formulations such as MS-Contin®),

d) with a bilateral, median and/or diffuse distribution, that cannot be relieved by surgical section of nocioceptive pathways (especially cervical cordotomy),

e) that can be relieved significantly by intrathecal administration of morphine.

The exclusion criteria are:

a) pain from sensory deafferentation such as post-root lesions of the brachial plexus, pain which does not respond to morphine or derivatives whatever the route of administration,

b) patients who have not received adequate doses of morphine via the oral route,

c) temporary or permanent contra-indication to implantation such as infection, suppurating bed-sores, coagulation disorders, etc.,

d) lack of consent from patient or family,

e) absence of a suitable medical or family environment for out-patient treatment and follow-up.

Two sites of intrathecal administration are used: lumbar puncture to spinal CSF, and directly into the cerebral ventricles. They are complementary, and their indications will depend essentially on the origin of the pain (subdiaphragmatic or otherwise).

3.1.3 Intrathecal Administration of Opiates via the Lumbar Route

This route is preferred for treatment of intractable cancer pain involving the lower half of the body. We will describe our experience, and discuss it in relation to other reports in the literature.

Patients

Between September 1978 and March 1990, 128 patients (76 male, 56 female) were selected for chronic spinal administration. The mean age was 61 years with a range of 35 to 80 years. All had become tolerant to oral or parenteral opiate agonists (60 to 300 mg/24 h; mean, 100 mg oral morphine/24 h). The duration of intractable pain before intrathecal administration ranged from 2 to 60 months (mean, 8 months).

The distribution of the primary malignant tumours was as follows: 73 pelvic (rectum 26, kidney 13, bladder 8, uterus 13, sacrum 2, prostate 11), 26 abdominal (colon 9, stomach 5, pancreas 11, retro-peritoneal leimyosarcoma 1), 9 cervico-thoracic (larynx 1, breast 3, lung 5). In 76 cases, the pain was secondary to regional involvement of lumbosacral plexuses. In others, the problem was essentially due to bone metastases (30 cases), visceral metastases (10 cases), or mixed lesions with invasion and metastases (12 cases).

Implantation Technique

The details concerning the implantation technique under local or neuroleptic analgesia are described in section 2.

Morphine solution and administration technique: The preservative-free morphine administered was a hyperbaric solution (7% dextrose) at a concentration of 5 mg/ml. Reservoir puncture was carried out using a fine needle (25 G) in a sterile technique. To check that the system is functioning correctly, 2 ml of cerebrospinal fluid (CSF) are withdrawn and retained for subsequent flushing of the reservoir after the morphine injection. The bolus of morphine is administered slowly into the reservoir. A 0.22 mm Millipore filter can be inserted between the syringe and the needle to ensure that the solution is free of bacteria. Serial CSF samples are then drawn for chemical and bacteriological analyses.

After administration, the patients were maintained in a 40–60° head-up position for 4 to 6 hours under routine cardiorespiratory monitoring

(apnea monitoring). Nursing staff must be prepared to reverse any occurrence of respiratory depression promptly with naloxone.

A low dose of morphine is given initially (2.5 mg). The doses are then progressively increased (5 mg, 7.5 mg, etc.) depending on the analgesia produced.

Results

Evaluation criteria: Analgesia was evaluated using a multifactorial clinical approach[63, 65, 69], based on the estimation of three pain-related criteria: 1) pain relief graded using a subjective linear scale; 2) impact on the patient's level of activity; (3) consumption of other analgesic drugs. Taken together, these three criteria provide a semi-quantitative evaluation of the analgesia obtained in any given patient. Side effects due to direct chronic spinal administration, such as central depression and tolerance, were monitored and noted as well as complications resulting from the implantation. One of us (B. S-C) was responsible for instructing the patient, the family members, and/or the nurses in charge of the out-patient treatment. She was also responsible for keeping in contact with them and their general physician.

Clinical response: The mean follow-up period for this series of 127 patients was 98 days (range 8–913). The mean initial daily dose of morphine was 2.5 mg (range 1.0–7.5 mg). All the patients reported significant analgesia within 5–20 min (mean latency 10 minutes), and pain relief lasted from 6 to 96 hours (mean, 32 h). During the course of treatment, the daily doses of morphine were increased moderately with a mean terminal daily dose of 5.5 mg (range 1.0 to 60 mg).

The final results (concerning the 127 now deceased patients) are: 102 cases of good and excellent results (80%), 21 moderate results (16.5%) and 4 failures (3%) with a mean follow-up of 3 months. We only observed two cases of significant tolerance. For one patient, the daily dose had to be increased from 2.5 mg to 60 mg to produce sufficient analgesia for a follow-up period of 159 days. For the other patient, the dose was increased from 2.5 mg to 50 mg over a 197 day follow-up period.

Fourteen other patients required a moderate increase in daily morphine [10 mg (10 cases), 15 mg (3 cases) and 20 mg (1 case)]. In the majority of cases (86%), analgesia was stable during the total follow-up period.

Side Effects of Morphine

Table 1 summarizes the side effects during the total follow-up (initial trial, titration period, and chronic administration).

The most common side effects were nausea and vomiting (45/128). The nausea generally subsided. In addition, 8 males presented urinary retention,

Table 1. *Morphine Side Effects After Lumbar Spinal Administration* (n = 128)

Nausea, vomiting	45
Constipation	1
Urinary retention	8
Dizziness	1
Drowsiness	12
Respiratory depression	5

which was transient in 7 cases. In one patient with a "bladder tumour", we replaced the morphine with an agonist, buprenorphin.

None of the patients, and in particular those in whom the follow-up was longest, developed any neurotoxic disorders secondary to the chronic intrathecal injection of morphine.

We saw 5 cases of central depression with drowsiness, myosis and respiratory disturbances. Three occurred during the initial test: in one case after administration of 5 mg of isobaric morphine at Th12, in another case after administration in the epidural space at Th6, and in the last case, after administration of 2 mg of isobaric morphine at Th5. These three spontaneously reversible complications did not require intubation or naloxone.

The fourth complication developed slowly in an out-patient implanted with a pump programmed to a continuous flow of 3.1 mg/day. The somnolence and respiratory depression were immediately reversed by naloxone. The pump was reprogrammed to a 2.5 mg/day bolus delay regimen without further incident. The fifth case occurred during the chronic administration period. The patient received 50 mg instead of 5 mg. This required intubation, and injection of naloxone.

In this series of 128 patients, we only had two local infections of the implant which had to be removed in one case. Purulent meningitis occurred in 8 cases, 4 during the initial trial, and 4 during chronic administration. In one case, the implant had to be removed. The others recovered after intrathecal administration of antibiotics via the implanted reservoir.

Discussion

In 128 patients suffering from chronic cancer pain intractable to oral or parenteral opiates (mean, 115 mg oral morphine per day), we obtained significant analgesia with low doses of morphine (1.0 mg to 7.5 mg) via the intrathecal route. There was a latency period of between 5 and 20 minutes, and pain relief lasted between 24 and 72 hours. Use of an hyperbaric solution of morphine (7% dextrose) increased the mean duration of analgesia[17]. These values are in good agreement with those of other authors[18, 25, 37, 78, 127]. The distribution of analgesia was metameric with a maximal caudal effect.

Among the 128 patients treated with spinal morphine, only 8 cases had thoracic or cervical cancer, but the location of the pain was always subdiaphragmatic, stemming from lumbosacral and iliac bone metastasis. In one case with cancer of the larynx and cervico-thoracic metastases, pain was only partially relieved after intrathecal morphine administration.

During the follow-up period (mean, 98 days) a steady increase in the daily doses (mean, 2.5 mg at the start and 5.5 mg at the end of the treatment) was needed to maintain the analgesic effects. These doses are comparable to those reported by other workers.

Transient siede effects such as nausea and vomiting, skin reactions and itching occurred frequently in the initial period of the treatment[33, 72, 86]. Transient urinary retention appears to be specific to spinal administration[68, 72, 90], while behavior disorders or mood swings are not observed.

The risk of central respiratory depression is low, as patients had already received significant amounts of oral or parenteral morphine. We noted 5 cases of respiratory depression. In three cases, central depressant complications occurred after intrathecal administration of an isobaric morphine solution as also reported by others[40]. In agreement with other authors[105, 125], we found that depressant effects may be reduced by administration of morphine in an hyperbaric solution with the patient in a 40–60° head-up position. In the other two cases, respiratory depression was due to overdosage. The choice between spinal intrathecal and intraventricular morphinotherapy will be discussed in section 3.1.4.

The future of this conservative and non-invasive method also relies on the development of new opioids activating different opiate receptors. During percutaneous intrathecal spinal screening, we tried the administration of pentazocine (5 mg) in 12 cases, and 1.13 or 1.10 amine dynorphin (100–200 g) in 5 cases. The results were disappointing. Recently, we have also tried buprenorphin in 11 patients during the initial period of intrathecal administration. The results were encouraging, and 5 terminally ill patients have been treated with this drug until their death.

However, use of this route of administration is in decline due to the introduction of new oral drugs such as Temgesic® (buprenorphin) or Moscontin® (slow-release morphine sulfate).

3.1.4 Intra-(cerebral)-ventricular Morphinotherapy

This is indicated essentially for pain with a supradiaphragmatic distribution such as that arising in cervicothoracic cancer, or the diffuse pain from metastases. This route of administration (ICV) can also be considered after failure of lumbar intrathecal administration for pain in the lower half of the back. We report our own results before discussion of the work of others.

Patients

From 1984 to April 1990, we selected 74 patients for chronic ICMV via an implanted access port. The age of the patients ranged from 40 to 80 years (mean, 62), and the duration of intractable pain before ICVM therapy ranged from 2–36 months (mean, 10 months). All were tolerant, oral or parenteral opiate agonists. The distribution of the primary malignant tumours and the distribution of the chronic pain were: 7 cases with diffuse bone or visceral metastases (2 kidney, 1 melanoma, 1 prostatic, 1 breast, 1 bladder and 1 vaginal); 22 cervico-cephalic cancers; 37 lung cancers with thoracic and upper limb pain; 8 abdominal or pelvic cancers. All eight patients with abdominal or pelvic cancer had sub-diaphragmatic pain, but there was a contra-indication or failure after spinal intrathecal administration of opioids via a lumbar access port.

Administration Technique and Morphine Titration

Using a sterile technique, the access port is percutaneously punctured using a 25 gauge needle connected to a 2.5 ml syringe. To check that the system is functioning correctly, 2 ml of cerebrospinal fluid (CSF) are withdrawn. This CSF sample is retained for flushing the access port after the injection of morphine. In case of doubt, the permeability of the device can be checked by injection of a contrast medium.

The preservative-free morphine sulfate solution (concentrations, 1 ml = 10 mg or 1 ml = 1 mg) is slowly adminstered from a 1 ml syringe. A 0.22 m Millipore filter can be inserted between the syringe and the needle to ensure that the solution is free of bacteria. Serial CSF samples are then drawn for chemical and bacteriological analyses.

In order to limit the risk of side effects and to gauge the efficiency, 0.125 mg of morphine is given as the first dose. Later, and according to the analgesia produced, the doses are progressively increased (0.25, 0.5, 1.0 mg, etc). The patients are kept under close neurological observation and cardio-respiratory monitoring (apnea monitoring) throughout this titration period. Nursing staff must be prepared to reverse any occurrence of respiratory depression promptly with naloxone.

Results

Evaluation criteria: Analgesia was evaluated using a multifactorial clinical approach[1, 20, 21], based on the estimation of three pain-related criteria: 1) pain relief graded using a subjective linear scale; 2) impact on the patient's level of activity; 3) consumption of other analgesic drugs. Taken together, these three criteria provide a "quantitative" evaluation in any given patient. Side effects due to direct chronic ICVM, such as central depression and

tolerance, were monitored and noted as well as complications resulting from the implantation. One of us (B. S-C) was responsible for instructing the patient, the family members, and/or the nurses in charge of the out-patient treatment. She was also responsible for keeping in contact with them and their general physician.

Clinical response: The mean follow-up period for this series of 74 patients was 75 days (range 12–230 days). The mean initial daily dose of morphine was 0.30 mg (range, 0.1–1 mg). All the patients reported significant analgesia within 5–60 min (mean latency, 20 min), and pain relief lasting from 12 to 70 hours (mean, 28 h). During the course of treatment, the daily dose of morphine was increased moderately. The mean terminal daily dose was 1.7 mg (range, 0.1–20 mg). However, the relative increase was quite low, since the ratio between the initial and terminal doses ranged from 1.26 to 3.41. The final results (concerning 74 now deceased patients) are: 62 cases of good and excellent analgesia (84%), 10 moderate analgesia (14%) and 2 failures (2%) with a mean follow-up period of 2.5 months. We only observed two cases of tolerance. One patient had been totally pain-free with 1 mg of morphine 32 days before the trial, but progressive increases in daily dose up to 20 mg did not induce analgesia. For another patient, the daily dose had to be raised from 0.5 mg to 15 mg to produce sufficient analgesia. Eleven other patients only required a moderate increase in daily morphine, never exceeding a four-fold increase of the initial therapeutic doses. In the majority of cases (61 cases), the analgesia was stable during the total follow-up period.

Side effects of morphine: Table 2 summarizes the side effects observed during the total follow-up period (initial trial, titration period and chronic administration).

Table 2. *Morphine Side Effects After Intra-cerebro-ventricular Administration* (n = 74)

	Titration period	Chronic administration	T
Withdrawal syndrome	0	0	0
Constipation	3		3
Urinary retention	1		1
Dizziness	5		5
Drowsiness	8	1	9
Myosis	3		3
Respiratory depression	2		2
Disorientation, euphoria	6		6
Hallucination, agitation	1		1

Minor morphine side effects (nausea, vomiting, constipation, urinary retention, itching, dizziness, headache, disorientation, euphoria or drowsiness) were initially observed but were short-lived. Some patients presented multiple side effects. We observed three major central side effects during the trial and titration period. In two cases, after administration of 1 and 1.5 mg of morphine, resepectively, the patients developed drowsiness, myosis and respiratory depression. A third patient presented visual hallucinations and behavioral disorders after an injection of 1 mg. These three central complications were immediately reversed by systemic naloxone with only a slight decrease in analgesia.

In this series of 75 patients, we only observed 3 complications due to local infection of the implant. In one case, the implant had to be removed, while the other two cases with transient purulent meningitis recovered after direct intraventricular administration of antibodies via the implanted reservoir. No patient presented CSF fistula.

Discussion

The time-course of ICVM analgesia was rather variable with a latency period of between 5 min and 30 min (mean, 15 min), to give a maximum intensity between 15 and 60 min after administration (mean, 25 min). The analgesia lasted for 12 to 72 hours (mean, 26 h). These values are in agreement with those reported by other authors[9, 74, 76, 86, 115]. The analgesia spreads rapidly throughout the body, particularly clear-cut in the patients with diffuse pain from widespread bone metastases. This effect has been reported by all authors, and it confirms the animal data on analgesia induced by intra-cerebral microinjections[1, 31, 73] or ICV administration[12, 13].

During the follow-up period, repeated ICV administration required a steady increase in the daily doses of morphine (on average 0.30 mg at the start and 1.7 mg at the end of treatment) to maintain the analgesic effects. The average daily doses of morphine administered, as well as the range of doses used at the start and end of treatment, were comparable to those reported in the literature (see Table 3) for similar follow-up periods. Only Obbens *et al.*[87] report the use of much higher doses, between 3 and 60 mg/24 h for an average follow-up period of 92 days. The doses required depended directly on the doses of systemic morphine used previously. They also report a more frequent development of tolerance. These results conflict with ours and those involving larger series[10, 74, 77, 115] (Table 4). The risk of central respiratory depression with ICVM is low[76, 102, 103, 115]. We only observed it twice during the initial titration period over a cumulative total of 5000 patient-days. Drowsiness was also rare (9 cases, 8 of which occurred in the initial period), in spite of the high doses sometimes used by the end of treatment. Behavioral disturbances such as hallucination and nervous-

ness, and mood swings were noted more often using this site of administration than after spinal administration[63, 69, 72, 86, 115]. Apart from initial and transient nausea or vomiting, digestive disturbances, constipation in particular, were short-lived, and ICVM did not have to be interrupted in any of the patients. We did not observe any cases of urinary retention which appears to be a directly spinal effect[45, 64, 68, 72, 80, 90, 117, 121, 124]. The lasting effectiveness and the low incidence of side effects are in general agreement with the literature data reported between 1982 and 1987[10, 12, 74, 76, 77, 86, 101, 102]. This is summarized in Tables 3 and 4.

In chronological order from 1982 to 1987, analysis of reports concerning ICVM shows that overall clinical experience, including our own, is still limited. Less than 300 cases have been published so far. Our disappointing experience with PVG stimulation[61] in eight patients suffering from chronic pain of neoplastic origin led us replace this technique with ICVM. In fact, in six cases with a significant follow-up period (3–12 months), there was a rapid development of tolerance (37 weeks) to deep brain stimulation which was not reversed of satisfactorily by simultaneous parenteral administration of serotoninergic drugs (L-tryptophan, 5-HTP or amitriptyline).Along with most authors[63, 68, 69], we believe that the choice between spinal intrathecal and intraventricular morphinotherapy depends essentially on the distribution of the pain. Table 3 shows that, excepting Obbens *et al.*[87], all authors restrict ICVM to the treatment of pain in the upper half of the body. Pain of this type generally stems from diffuse, cervicocephalic and thoracic cancers, or abdomino-pelvic cancers with metastases. The latter may not respond to spinal intrathecal morphinotherapy. How-

Table 3. *ICVM – Literature Data in Chronological Order*
A) Topography of Pain of Cancerous Origin

	n	Diffuse metastases	Cervico-facial	Thoracic	Abdomino-pelvian
Leavens *et al.*	4	—	—	—	4
Lobato *et al.*	44	12	19	4	9
Roquefeuil *et al.*	8	3	1	3	1
Nurchi	5	3	2	—	—
Thiebaud *et al.*	32	6	16	2	8
Lenzi *et al.*	38	5	29	4	—
Blond *et al.*	79	19	58	2	—
Obbens *et al.*	20	—	—	—	20
Lazorthes and Verdié	74	7	22	37	8
Total	304	55	147	52	50

Table 4. *ICVM – Literature Data*
B) Daily Doses, Follow-up and Results

	n	Doses (mg) min – max	Follow-up (days)		Analgesia (B + E) (%)	Tolerance	Side-effects	
			range	ave.			respir.	vigil
Leavens *et al.*	4	0.5–7	2–90	85	75	1	—	–
Lobato *et al.*	44	0.25–16	6–150	55	97	—	3	3
Roquefeuil *et al.*	8	0.4 – 7	8–120	73	80	1	—	2
Nurchi	5	2–4	8–48		100	—	1	—
Thiebaud *et al.*	32	0.10–15	4–230	50	90	9	1	6
Lenzi *et al.*	38	0.5–2	4–292	65	95	—	1	5
Blond *et al.*	79	0.05–3	3–132	65	94	—	2	—
Obbens *et al.*	20	3–60	7–510	98	> 50	+ + +	—	3
Lazorthes and Verdie	74	0.10–20	12–230	75	84	2	2	2

ever, for chronic pain of cancerous origin in the lower half of the body, we prefer, for both ethical and clinical reasons, to start with intrathecal morphinotherapy.

Although the effectiveness of the analgesia from ICVM is undoubied, the neurophysiological mechanism is still unclear. If the effect is purely supraspinal, we do not know which descending control systems modulate the input of the nocioceptive messages to the spinal cord[69]. It is thought that ICV-administered morphine acts directly on central structures rich in opiate receptor sites, and that these structures influence the descending pathways originating in the brain stem which inhibit neurons of the dorsal horn[12].

We feel that the intense and diffuse analgesia reported with ICMV is independent of any direct action of morphine which might have diffused to the spine. This is supported by the following observations:

1) The time-course and the topography of ICVM analgesia is different from that observed after spinal morphinotherapy[67, 69].

2) HPLC assay of morphine in lumbar CSF after ICV administration showed that perispinal diffusion occurs after the development of analgesia, and that the amounts diffused were not sufficient to induce direct spinal analgesia[8]. Thus, in a patient with two intrathecal access sites (one in the lateral ventricle and the other lumbar), repeated ICV administration of 1.0 then 1.5 mg of morphine did not lead to significant concentrations of morphine in spinal CSF 1 h after ICV injection.

3) The kinetics of ICV-administered radiolabelled iodomorphine showed that: (a) the radioactivity migrated very slowly, (b) after 1 h (i.e. after the maximum latency of development of analgesia) only 5% of the injected dose had left the cerebral ventricles, and (c) the drug did not diffuse beyond the thoracic region[114].

3.1.5 Conclusion – Perspectives

The use of morphinotherapy by intra-ventricular (ICVM) administration for treatment of chronic intractable pain of cancerous origin is supported by recent fundamental data. This new method has aroused considerable clinical interest not only because it is effective, but also because it is relatively non-invasive, and the drug effect is reversible. It now forms part of the panoply of modern neurosurgical techniques involving activation of neurophysiological control mechanisms.

In patients who have become tolerant to large doses of parenterally administered morphine, ICVM produces fast and complete analgesia at low doses. Tolerance with ICVM is reduced since the mean terminal daily dose is 1.5 mg in the various published series. Although the site of administration is central, the side effects, especially central depression, are mod-

erate. They are generally observed in the initial period and are rapidly reversible. There is, however,a potential risk with this technique, and patients must be carefully monitored. The intra-ventricular route of administration is complimentary to the lumbar intrathecal route, and the choice of route will depend mainly on the site of the pain. ICVM is particularly indicated for chronic neoplastic pain of cervico-cephalic, thoracic or diffuse origin arising from widespread bone metastases.

3.2 Intrathecal Baclofen for Control of Severe Spasticity

3.2.1 Neurochemical and Pharmacokinetic Basis

For the last 20 years, Baclofen (Lioresal®) has been the most widely used antispastic drug, especially in the treatment of motor and spastic syndromes, notably of spinal origin[27, 122]. Its effect on the increased muscle tone and spinal neuron hyper-excitability is attributed mainly to its ability to block the release of neurotransmitters at spinal synapses[128]. Baclofen is a specific agonist of gamma-aminobutyric acid B receptors which are abundant in the superficial layers of the spinal cord[15, 16, 100]. When given orally, Baclofen does not readily penetrate the blood-brain barrier[55, 56], and it is distributed equally to the brain and spinal cord, giving rise to side effects at therapeutic doses, of which the most troublesome is somnolence. To get round these obstacles, Penn[58, 91, 92] pioneered direct intrathecal administration of this drug for the treatment of severe spasticity. This was aimed at direct activation of GABA-B receptors by preferential perfusion in the spinal cord in an attempt to limit the central effects.

3.2.2 Patient Selection Criteria

Clinical pre-selection was based on the following criteria:

Cases of severe invalidating spasticity secondary to a stable spinal cord or cerebral lesion itself secondary to:

– lesion of traumatic origin (para, tetra or hemiplegia),

– a demyelinating spinal disease such as multiple sclerosis specially in its slowly progressive spinal form,

– or a motor disability of cerebral origin with spastic predominance.

Failure of medical treatment, and notably of oral Baclofen administration over a protracted period. Usually, it is the occurrence of unacceptable side effects (constant drowsiness and confusion) which limits an increase in oral dose. In the present study, all the patients were taking around 90 mg of Baclofen (60–100 mg) per 24 hours in association with other anti-spastic drugs such as diazepam and sodium dantrolene without any effect on their spastic and motor syndrome.

Absence of contra-indications for pharmacological reasons (vis-à-vis Baclofen), or psychological or local reasons such as bed-sores or skin lesions in the lumbo-abdomino-pelvic region which preclude the percutaneous implantation of a catheter or drug delivery system. It is essential that conditions (limb bed-sores, urinary infections, etc). which, though they may not interfere with the implantation site, can aggravate the spastic syndrome, be treated before any intrathecal pharmacological trial.

Consent from the patient clearly informed as to the constraints of the method (regular consultations, adaptation of dose, etc.) and therapeutic limitations.

Finally, the patient must be in an environment (family, general practitioner or institution) that is favorable to regular follow-up as an out-patient.

After clinical evaluation, the definitive selection is confirmed by a test lumbar intrathecal administration of Baclofen. This preliminary trial is an essential step before considering chronic out-patient treatment. It is carried out in the homes of patients who satisfy the clinical criteria for inclusion, and is designed to test individual tolerance, to judge the efficiency of intrathecal administration, and to fix the effective dose of Baclofen for an 8–12 hour action. This test period often needs to be prolonged for several days, and sometimes for a few weeks. We therefore replaced the initial use of an externalized lumbar sub-arachnoid catheter by systematic implantation of a lumbar intrathecal access site (Cordis Multipurpose Access Port, or Miniport) allowing prolonged testing. The risk of complications (CSF leakage, headache from intracranial hypotension, meningitis, etc.) or secondary displacement using percutaneous sub-arachnoid catheters clearly increases with duration of the trial. Experience has also shown that it is preferable to wait for a few days, and even up to complete healing of the implant incision, before starting intrathecal administration tests. Simply implanting the catheter and the port can aggravate spasticity for several days, and thus affect the results of the first pharmacological tests. Progressive dose tests must be run as soon as the clinical condition stabilized. Whatever the previous oral dose of Baclofen, the first intrathecal dose must be low in order to evaluate individual tolerance. We usually gave a first bolus dose of 25 μg, and then steadily increased the dose, generally by 25 μg per day until a dose was reached which produced an effect for 8–12 hours. The test administration can be carried out either by repeated bolus doses, or by perfusion with a portable external pump. Clinical evaluation of the results by muscular testing is gauged by systematic exploration of the H reflex. At the end of the trials, the lumbar intrathecal access port was left in position. This was used for subsequent sampling of the CSF not only for cytobacteriological examination but also for pharmacokinetic study (HPLC assay) to check the steady-state intrathecal levels of Baclofen[104].

Out of 43 patients receiving intrathecal Baclofen, 21 were selected for chronic administration. Most of these patients (17/21) suffered from spasticity of spinal origin: 8 presented multiple sclerosis of the spinal form which was fairly stable, 8 others had spinal trauma, there was one case of spinal ischaemia secondary to a diving accident, and another case was secondary to transverse myelitis. The 3 other patients selected for chronic Baclofen treatment presented spasticity of cerebral origin: one case of cerebral palsy, one case of traumatic cerebral lesion and one spastic syndrome arising from hemiplegia of cerebro-vascular origin. The age of the patients ranged from 14 to 70 years (mean, 35 years). There were 12 men and 8 women.

Three of the first patients selected had been treated without success by chronic cervical spinal cord stimulation. Thus 22 spastic and motor syndromes tested by short-term intrathecal administration were excluded for chronic administration. The exclusion factors were either ineffectiveness of intrathecal administration or over-effectiveness with loss of useful spasticity of the lower limbs enabling the patient to stand and walk to a certain extent, or a reduction in residual motor performance of the upper limbs. Finally, other patients were rejected because of foreseeable difficulties in follow-up, or lack of conset.

3.2.3 Implantation for Chronic Intrathecal Administration, Titration and Out-patient Follow-up

We employed various implantable drug-release systems in this series of patients. The lumbar intrathecal access port used for the test was also used for chronic administration in the first 6 patients. This required repeated daily injections with its inherent inaccuracy in dosage and appreciable risk of infection. We have now gone over to implantable programmable drug-release systems that allow accurate administration of the titrated individual dose of Baclofen. The last 15 patients have thus benefitted from implantation of a Synchromed system. The implantation technique is simple, and can be performed percutaneously under local anaesthetic, although in some patients, implantation was carried out under general anaesthetic either at their request or because of excessive muscular spasm in flexion. The simplicity of the surgical technique of implantation does not, however, mean that technical precautions can be ignored, especially concerning the positioning of the subarachnoid catheter. The intervertebral space is generally punctured at the lower lumbar level (L3/L4/L5) in order to introduce the catheter far enough into the subarachnoid spaces to avoid secondary displacement. The distal end of the catheter under fluoroscopic guidance is usually placed at the level of the lumbar enlargement, i.e. between Th10

and L1. The exit of the catheter from the superficial lumbar layers must be carefully fixed to the subcutaneous or fascial tissue to avoid displacement and stenosis. The proximal end of the catheter is tunnelled under the skin, and linked to the drug pump which is implanted in a subcutaneous site, usually in the abdominal wall, but occasionally in a lateral thoracic position.

For safety reasons, the initial dose administered immediately after implantation was twice the effective 8-hour dose determined during the intrathecal selection test. Baclofen, supplied by Ciba-Geigy Laboratories as a intrathecally-administrable solution was used at 3 concentrations, either 50 μg/ml (during the test period) either 500 or 2000 μg/ml (during the period of titration and chronic administration). During the first weeks, the dose was steadily increased in steps of 10–20% of the daily dose depending on the clinical response and the effect on the H reflex. We observed a considerable inter-individual difference in the initial efficient daily dose (15 to 250 μg/24 h); mean, 90 μg/24 h). After determination and stabilization of the initial efficient daily dose, adjustments must be made periodically as a function of clinical response and incidence of side effects. This step is particularly important, and it relies on efficient coordination of the care team. A pharmacist in our team is responsible for liaison between our laboratory, the patients and their family and medical environment. The patients come in for regular consultations either as scheduled or if the alarm beep warns them that the pump reservoir needs filling within the following week. The residual volume that sets off the alarm system is fixed according to the daily consumption of the individual patient. Daily consumption increased moderately during the first months of treatment before stabilizing to an average of 190 μg/24 h (range, 26 to 500 μg/24 h). The maximum useful volume of the reservoir is 18 ml with a Baclofen concentration of 500 μg/ml. More recently, a concentration of 2000 μg/ml has been employed, so the period between refills varied considerably between patients. At each consultation, adjustments of the therapeutic dose were sometimes required in the light of the clinical and functional findings. The patients were informed about possible side effects, and the risks of overdose. Owing to the absence of antagonists specific for Baclofen, it is essential that the patients are aware of the first signs, i.e. excessive salivation, dizziness, nausea and/or vomiting, excessive muscular hypotonia spreading to the upper limbs, progressive difficulty in concentration with somnolence. A large overdose of Baclofen leads to respiratory depression and coma. Apart from a mechanical failure in the drug delivery system producing a sudden increase in delivery, overdose phenomena develop slowly, usually over a period of several hours or even days. If the patient is relatively close to the hospital, there is generally enough time for a forewarned patient and an informed family to come and have the dosage adjusted, or if necessary, the pump stopped and the reservoir emptied.

The clinical response was based on objective assessment of both the spasticity and the functional improvement. Spasticity was evaluated by scoring muscular hypertonus on Ashworth's scale[94, 97], although tendon retraction may hamper accurate evaluation. The frequency of painful spasms was noted during the clinical examination. Tendon and plantar reflexes were also determined. Functional improvement was evaluated on a scale scoring the different motor performances. The scale was derived from that proposed by Davis[29] for evaluation of the motor performance of motor invalids with cortical involvement. This scoring system was used successfully in a similar situation[110], and so we employed it to evaluate functional improvement. This was split into 3 levels: marked improvement (> 3), moderate improvement (between 1 and 3) and no improvement (0).

The Ashworth Scale

1. No increase in tone
2. Slight increase in tone, giving a "catch" when affected part(s) moved in flexion or extension.
3. More marked increase in tone but affected part(s) easily flexed.
4. Considerable increase in tone, passive movement difficult.
5. Affected part(s) rigid in flexion or extension.

Neurophysiological exploration of the Hoffman reflex (ratio H max/M max) was also employed to back-up the clinical assessment of hypertonia. This was measured using various procedures. During the test period, the H-reflex was measured before and after a bolus intrathecal injection. After implantation and during dose titration, the H-reflex was monitored semi-continuously during a rapid or slow infusion of the efficient therapeutic dose. Results were related to the clinical response. The H-reflex was also measured at out-patient follow-up in order to adjust therapy to individual functional targets, and keep the M max/H max ratio to within normal limits ($\leqslant 50\%$).

3.2.4 Clinical Results

3.2.4.1 Administration of a Single Intrathecal Bolus of Baclofen

Single bolus administration was employed during the test period, and only exceptionally during chronic treatment. In the latter case, the patient requires successive bolus injections (bolus delay) which assumes that the patient has reached his basal clinical state between two consecutive boluses. This rarely occurs in practice. In fact after a single lumbar intrathecal bolus, the latency of a clinical effect is relatively long (around 1 hour), and it affects the lower limbs first. Subsequently there is rapid development

(about 15 min) with a drop in muscular hypertonia, progressive disappearance of tone and a somewhat delayed decrease in tendon reflexes. Babinski's sign, or the plantar reflex in extension, is the last to disappear. The intensity, the metameric topographic extent as well as the duration of the clinical effect depend on the dose administered and on the individual patient. The efficiency of an individual dose is based on clinical criteria since in some cases, full hypotonus of the lower limbs should be avoided in order to maintain "useful spasticity" of the extensor muscles.

3.2.4.2 Results After Chronic Administration

Our results only concern the first 18 patients selected and implanted for chronic intrathecal administration over the period from May 1984 to December 1988. The mean follow-up was 28 months (range 4 to 56 months). In all the patients, muscular spasticity improved significantly. All the patients were selected at clinical stage 4 (5 patients) or 5 (13 patients) on Ashworth's scale. After treatment for various lengths of time, all patients presented a decrease in muscular hypertonia: 4 patients at stage 1, 12 patients at stage 2, and 2 patients at stage 3. The improvement in spasticity was observed during the titration period, and remained stable thereafter. Moreover, an improvement was seen in 14 out of 16 patients with painful muscle spasms.

Functional improvement varied considerably between patients, and depended on both the clinical stage and the etiology. Long-lasting functional improvement was observed in 3 patients including a 26 year-old bedridden Th8 paraplegic who recovered full autonomy within the space of three years. He was able to carry out basic tasks, get about in a wheelchair and even to stand and walk with a walking frame. This stable improvement was induced by a continuous slow intrathecal administration of Baclofen (26 µg/24 h). Functional improvement was moderate in 9 other patients, although in 3 of them it could be regarded as a marked improvement. Treatment had to be interrupted in case 5, a 56 year-old C6 tetraplegic, despite an excellent initial clinical response, due to local sepsis complicated by transient meningitis. The access port had to be removed after 26 months, and there was some delay before a Synchromed system was implanted. Case 11, a 27 year-old complete Th4 paraplegic, increased autonomy and improved use of his wheelchair, but did not retain any residual motor function. Case 14 with minor paraparesis secondary to spinal ischaemia from a dividing accident, with effort-induced distal spasticity of the posterior muscles of the leg, was cured of the spasticity, but the initial handicap was slight, his functional category was not altered.

The last 6 patients showed no functional improvement. They were all severely handicapped, bedridden and presented with tendon retraction.

Improvement in these cases was gauged essentially in terms of nursing requirements. Four of these patients had multiple sclerosis. The most common etiology in our patients selected was spasticity of spinal origin either due to trauma (7 patients) or the degenerative myelopathy of multiple sclerosis (6 patients). Comparing the results obtained in these two subgroups of patients, the most significant and stable improvements were observed in spasticity of post-traumatic origin, especially the cases of incomplete paraplegia. In these patients, there was both improvement in the spasticity and functional gain. The only patient without functional improvement was a 29 year-old full C5 tetraplegic (case 7), although he had a reduction in spasticity with suppression of painful spasms, and thus an improvement in nursing comfort.

In the 6 patients with spinal spasticity secondary to multiple sclerosis however, the results were less favorable. Spasticity was consistently reduced and in some cases completely suppressed, but there was little actual functional improvement (good in 1 case, moderate in 1 case and nil in 4 cases). This lack of improvement stemmed essentially from the gravity of the initial state and the absence of residual motor function. Moreover, although the selection criteria used were those of stable demyelinating disease, this is a progressive disease and the spinal deficit is commonly associated with supraspinal impairment such as a cerebellar syndrome which augments the handicap. In addition these patients were generally referred to us at a late stage when they had become bedridden with irremediable tendon retraction which effectively compromised functional improvement.

3.2.4.3 Complications

Side effects may be of technical, neurological or pharmacological origin, and they represent a very real risk for this type of therapy. A rigorous methodology must therefore be employed with careful follow-up.

The technical complications included 3 cases with displacement of the catheter from the sub-arachnoid space towards the epidural or extra-spinal space. This occurred in patients implanted with access ports (cases 1, 2, 3). The initial sign of a complication was lack of effectiveness of the intrathecal Baclofen, confirmed by administration of a radio-opaque substance via the access port. In all cases, the catheter was repositioned with resumption of response to a previously established effective dose. Two patients, who were initially treated with a mechanically activated Secor pump delivering isolated bolus doses, had to have the device removed as there was imprecision in dosage. These patients (cases 7 and 9) were subsequently implanted with programmable Synchromed pumps with a successful resumption of treatment. Lastly, one patient, the only motor invalid of cerebral origin in this series (case 8), received an overdose due to a pump failure which led

to respiratory depression and temporary coma. The pump had to be stopped in emergency and removed. In this case, the pump was a first generation programmable device (DAS system from Medtronic) which was implanted in September 1984, and which had operated perfectly for over a year.

Infections and Neurological Complications

We observed 4 cases of local sepsis around the subcutaneously implanted drug delivery systems, and 3 cases of temporary meningitis. There were no neurological complications. Of the 4 patients with subcutaneous sepsis, 3 were implanted with access ports (cases 2, 5, 6), and so required repeated daily percutaneous injections. The fourth patient, a case of severe immunodepressive multiple sclerosis (case 9) had a Synchromed system. Six months previously, she had developed temporary meningitis during a preliminary treatment phase via an access port. Although the implantable pump had not been implanted in the same place (abdominal instead of lateral thoracic site), secondary infection could not be prevented. The patient was bedridden and suffered from recurrent urinary infections.

Purulent meningitis was observed in 3 patients. This was treated by both local (via the access port) and systemic (i.v.) antibiotics. In 2 of these patients (cases 9 and 14), the meningitis established during the initial trial with the access port was isolated and there was no subcutaneous sepsis. On recovery, intrathecal treatment was resumed either temporarily (case 9) or permanently (case 14) via an implantable Synchromed pump. The third patient (case 5) developed purulent meningitis along with subcutaneous sepsis and removal of the access port was required before recovery took place. In this patient, who had an excellent response to intrathecal therapy, implantation of a programmable pump is planned as soon as the cerebrospinal fluid is clear of infection.

In summary, although the occurrence of local sepsis always led to removal of the access port and temporary or permanent interruption of intrathecal administration, the isolated occurrence of purulent meningitis did not stop the treatment program (cases 9 and 14). All the cases of infection whether local or meningeal were observed in patients treated via access ports. The increased risk of infection arising from daily percutaneous injections in immunodepressed patients finally led us to abandon this method of administration in favor of the now systematic use of implantable programmable pumps..

Pharmacological Complications

These represent an intrinsic risk of this method and are seen as an over-efficiency, an overdose, or a losee of efficiency due to acquired tolerance. Detrimental transitory muscular hypotonia was one of the most frequent

therapeutic reasons for non-selection during the initial trial period. Some patients were rejected for chronic treatment, as the over-efficiency of intrathecal Baclofen abolished useful spasticity in the lower limbs, or reduced motor performance in the upper limbs.

In the initial titration phase, we observed muscular hypotonia in 5 patients. Three of these patients were treated via an access port, but we could not be sure that all or part of the dose had actually been administered, even though the access port was flushed after each administration. In two other patients treated via a Synchromed system, the transitory hypotonia was rapidly counteracted during the titration period. This highlights the necessity for exact tailoring of dosage. We believe that the required accuracy can only be achieved using programmable implantable pumps.

A minor overdose leading to diffuse muscular hypotonia with temporary drowsiness was observed in 4 patients, 3 of whom were being treated via an access port. This arose during the titration period, and did not recur during the period of out-patient treatment after establishment of the efficient daily therapeutic dose.

Serious overdose causing progressive respiratory depression and transient coma occurred in two patients. In one of the patients (case 8), this was due to malfunction of the pump. The coma and respiratory depression were corrected by respiratory resuscitation with intubation, repeated lumbar puncture and i.v. hydration to accelerate renal elimination of Baclofen. The pump was stopped in emergency and removed. Treatment was not resumed in this patient In the other patient (case 1), with advanced multiple sclerosis, the overdose occurred after a bolus administration of 200 µg of Baclofen into the access port. The moderate respiratory depression and coma reversed spontaneously without the need for respiratory resuscitation in intensive care. Accidents of this sort can now be avoided by interruption of intrathecal administration and i.v. injection of physostigmine.

Acquired Tolerance

After the titration period, the dose of Baclofen was usually adjusted every 24 hours. The dose increment varied greatly from one patient to another, although efficient stable doses were obtained within three months. We have yet to observe a genuine case of pharmacological tolerance.

3.2.5 Discussion

Our results confirm the efficiency of this type of administration in patients suffering from an invalidating spastic syndrome that in intractable to long-term oral anti-spastic therapy. All our patients had previously been treated with high doses of Baclofen (60 to 100 mg/24 h) in association with sodium

dantrolene which in many cases was associated with diazepam. This treatment had become inefficient with side effects such as somnolence, and confusion.

3.2.5.1 Inter-individual Differences in Dose

The pharmacological tolerance observed during oral administration was overcome by intrathecal administration since very low doses could be employed. Typically, the therapeutic effect was obtained, after the titration period, for an average dose of 90 µg of Baclofen. We did, however, observe considerable inter-individual variation in threshold of efficiency (15 to 250 µg).

During the initial trial period with bolus intrathecal administration the effects of the drug were only felt after a latenty period of from 45 to 60 minutes. This was presumably the time required for Baclofen to diffuse passively through CSF to the dorsal spinal root junction via the Virchow Robin cisternae, and finally bind to GABA-B receptors in the superficial layers (Rexed, 1 to 4) of the dorsal horn. This is a fairly long delay considering that the anatomical distance is only a few millimeters. It may be a result of the low liposolubility of Baclofen. After the latenty period, the effects set in rapidly with a peak response 15 minutes later. We observed a decrease in the muscular hypertonia with a progressive disappearance of the clonus and the monosynaptic tendon reflexes and finally loss of the Babinski's sign. Muscle tone and reflexes can be entirely abolished with larger doses. Baclofen distributes rapidly in CSF, but to a variable height with a predominantly caudal, metameric action, depending on the local concentration. The duration of the effect is variable albeit dose-dependent, and symptoms reappear in the reverse order and just as rapidly. The effect is perfectly reproduced after a new administration.

These observations were reported after the first trials of Penn[91, 92, 96] and have been confirmed by various authors[43, 66, 67, 71, 81, 82, 94, 97, 110]. In the present study (n = 18), the follow-up period (on average 28 months) and the long-term results are sufficient to demonstrate a stable clinical response without acquired tolerance. In all patients, we noted that the 24-hour doses had to be steadily increased during the first month of treatment, remaining stable thereafter. The average efficient dose rose from 90 to 190 µg for a range of individual values between 26 an 500 µg. These results are comparable to those of Penn[93, 94, 96, 97] who found that in a series of 20 patients, the initial average efficient dose increased from 150 to 340 µg (range, 62 to 749). Müller *et al.*[82], in a series of 25 patients with an average follow-up period of 2 years, reported an increase in the average daily dose from 234 to 294 µg. All authors noted a marked inter-individual variability of the efficient therapeutic dose. In our series, it was of the order of 1 to 20.

Penn[94] reported a 1 to 30 ratio whereas for Müller and Zierski[82] it was 1 to 80 (10 to 800 µg). This variability can be accounted for by differences in enzyme-mediated metabolism, local clearance by recirculation, and range and extent of the spinal lesions. This stresses once again the importance of accurate dosage which must be carefully adjusted in accordance with the therapeutic objectives which will also differ from one patient to another. They depend on the clinical stage of the condition, and whether the desired effect is total abolition of spasticity in patients who have lost all motor activity, or partial reduction of spasticity aimed at conservation of a certain degree of useful spasticity in patients with some functional motor activity. In order to optimize dosage, we were guided, not only by the clinical response, but also by the quantitative changes in Hoffmann's monosynaptic reflex (H reflex) and CSF Baclofen levels.

The ratio M max/H max determined at each consultation, is an index of efficiency which may also be taken into account in the light of therapeutic goals. For example, after a bolus intrathecal lumbar injection (50 to 75 µg of Baclofen) to six patients with longstanding spasticity and impaired voluntary motor control, Latash and his colleagues[59] demonstrated that the dramatic suppression of the spastic signs was accompanied by more selective voluntary muscle activation. Tonic coactivation of the antagonists and distant muscle groups during voluntary contraction was decreased, while the agonist level on electromyography (EMG) was not affected (3 cases) or only slightly reduced (3 cases). Furthermore, in one patient with sufficient residual motor control, there was a considerable increase in the speed of fast isotonic movements, accompanied by the emergence of the ability to generate phasic muscle bursts on EMG that were characteristic of normal motor pathways. This suggests that Baclofen exerts different effects upon reflex pathways and descending motor pathways, and demonstrates that elimination of spasticity may also improve voluntary motor function in some patients.

3.2.5.2 Influence of Etiology on Functional Improvement

Analysis of the results showed that the efficacy depended on both the etiology of the spasticity and the clinical stage of disability. From the clinical findings and the results of the trials using repeated bolus doses, we found, in agreement with other authors, a greater effect on spasticity of spinal origin whether post-traumatic or secondary to demyelinating disease. In fact we found that the effect on spasticity and painful muscular spasm was more or less identical in the two subpopulations, but functional improvement was greater in trauma cases with spinal lesions, and in patients with stabilized neurological lesions and deficits below the level of the lesion. In multiple sclerosis, the progressive character and the associated spinal lesion of a higher level tend to enhance the handicap and reduce the

functional improvement. The severity of the clinical stage also accentuates this difference. Initially, this therapy was restricted to the advanced, highly disabling clinical forms, such as bedridden patients or those with restricted freedom of movement. In these clinical forms, the motor deficit is complete below the lesion irreversible tendon retraction is common, and the only functional benefit concerns nursing comfort and suppression of painful muscle spasms. This was the case for 7 of our patients, 2 of whom had post-traumatic cervical or cerebral lesions, and the other 5 had multiple sclerosis.

Subsequently, patients with less serious clinical features were selected. In these patients, independence of movement and motor performance are reduced owing to the intractable nature of the spastic syndrome, and therapy is aimed at improving both comfort and autonomy. This is reflected by greater independence in a wheelchair with sometimes a real functional improvement in the motor performance of the arms, or walking with the aid of a frame, when there is residual motor function of the lower limbs with "useful spasticity". This was the situation for 8 of our patients, 4 of whom were suffering from spinal post-traumatic lesions at the thoracic level. For these patients, the functional gain was secondary to both reduction in spasm and improved motor control. Latash *et al.*[59] has also reported an unmasking of motor control by intrathecal Baclofen, although the degree of improvement does not appear to be predictable before intrathecal drug administration.

Future indications for this mode of administration will probably extend to minor clinical forms in fully autonomous patients with disabling effort-induced spasticity sometimes accompanied by painful spasms, especially at night. The problem here is essentially that of accurate dose adjustment in order to normalize muscle tone with conservation of adequate motor function and extensor tone for standing or walking. Dosage can now be adjusted with some precision using implantable programmable pumps like the Synchromed. Complex infusion cycles can be programmed allowing administration of higher doses at night to counteract painful spasm without interfering with motor function during the day. This was the case for two of our patients. In one of them, the distal effort-induced hypertonus was suppressed with no concomitant disturbance of motor function.

However, the spastic syndrome is not static, and numerous intrinsic factors (infections, asthenia, etc.) or extrinsic factors (changes in the weather, temperature, atmospheric pressure, travelling, etc.) can aggravate the condition, requiring temporary adjustment of the intrathecal treatment regimen. Although the implantable programmable systems available at present (Synchromed for example) can be programmed at the treatment center, there is no provision for the patient to self-prescribe a predetermined extra dose in the event of fluctuation in the spasticity.

The risks of direct intrathecal perfusion of Baclofen have been stressed by all authors, although technical risks should not be confounded with pharmacological risks. The mechanical complications were reported mainly during the initial period of development of the technique. Steady technological progress over the years has already solved many of these problems, and those remaining are likely to be overcome in the near future. We feel that access ports should be abandoned for chronic treatment, but they are indispensable for the prolonged trials during the selection period. We have also found it useful to leave the port in place during chronic treatment for removal of CSF samples if necessary. Along with other authors[53, 82, 94], we found that continuous intrathecal administration gave better results than administration by repeated injection. Of the 11 patients implanted with the Synchromed system, only one showed a better clinical response to daily bolus administration at a fixed time (9.00 a.m.). In the other patients, a better balance of the spastic and motor syndrome was obtained with continuous infusion.

3.2.5.3 Pharmacological Complications and Risks

Pharmacological complications represent the potential risks involved with this method, and they can detract from its value. Oral Baclofen is evenly distributed in the brain and spinal cord but its anti-spastic action is essentially at the spinal level. Increasing the dose via the systemic route thus leads to central side effects such as drowsiness, and confusion. Local intrathecal administration leads to a preferential perfusion of the spinal cord, although since the subarachnoid spinal and cerebral CSF compartments are continuous, central side effects can also occur with this route of administration. Our results, as well as the experience of others highlight the marked inter-individual variability in effective therapeutic doses (between 26 and 500 µg in our series), and the importance of optimal individual titration. This variability is accounted for by different rates of passive diffusion in both CSF and at the posterior spinal root junction, and differences in catabolic activity. There are also likely to be considerable differences in degree and extent of the lesions between patients. The half-like of Baclofen in the CSF is between 4 and 5 hours[96, 100]. In the event of an overdose, 30 to 40 ml of CSF can be withdrawn by lumbar puncture, or via the access port, for a quicker reduction in adverse reactions. Although it is not a specific antagonist of Baclofen, intravenous physostigmine (1 to 2 mg over 5 min) can counter its central effects, especially the drowsiness and respiratory depression[83]. It is therefore an effective antidote and improves the safety of the technique. However, it should be noted that physostigmine has a short half-life in CSF, and it may be necessary to repeat a 1 mg i.v. injection every 30 to 60 minutes. A specific antagonist Baclofen

has recently been reported to antagonzie both the peripheral and central effects of Baclofen[54]. Delta aminovaleric acid has also been shown to have an antagonist action in the central nervous system[107]. The future availability of specific Baclofen antagonists will undoubtedly improve the safety of the technique.

3.2.5.4 Alternatives to Intrathecal Baclofen

Whether administered intrathecally or systemically, Baclofen is the most effective anti-spastic drug to date. However, during the percutaneous trial period (in 5 patients) and the chronic administration period (in 3 patients), we compared it to both morphine and midazolan. Intrathecal morphine has been proposed for control of spasticity[34]. With a follow-up period of 1 to 7 months, Erickson reported a significant response in spasticity of post-traumatic origin. Morphine is a non-specific opiate agonist of μ receptors. Its action is dose-dependent, selective, and it affects nociception and polysynaptic reflexes. Willer reported that intrathecal administration did not lead to any objective modification in the motor function or gamma monosynaptic reflexes in voluntary paraplegics[126]. In our series, we noted an overall decrease of spasticity, but it was quite moderate compared to the effect of Baclofen. In 3 patients treated over a 2 to 3 months period, we observed a falling off in clinical response, progressive urinary retention and acquisition of tolerance. We therefore discontinued intrathecal morphine whose only advantage is the availability of a specific antagonist, naloxone.

Midazolan is a water-soluble benzodiazepine that can be administered intrathecally, and it has been employed in the treatment of spasticity[66]. The clinical effect is moderate and rather short-lived as the biological half-life is around 2 hours. High doses provide no additional therapeutic effect and lead to somnolence.

The place of intrathecal Baclofen in the treatment of spasticity still remains to be established, while controversy still surrounds the surgical treatment of this condition[53]. Chronic electrical stimulation of the spinal cord has been used in the treatment of spasticity of post-traumatic origin or that arising from demyelinating disease[21], while stimulation of the anterior cerebellum has been applied in spastic and motor syndromes of cerebral origin[22, 29, 62, 123]. Chronic neurostimulation of the spinal cord or cerebellum is a conservative method, only slightly invasive, is totally reversible and is founded on neurphysiological principles[108, 109]. However, its immediate effectiveness is moderate with little clinical or neurophysiological response[89]. There is also a lack of appreciable long-term functional improvement. The relatively low efficiency of electrical neurostimulation led us to abandon it in favor of intrathecal Baclofen administration in the treatment of severe spasticity of spinal origin[109].

Functional neurosurgery for spasticity commenced as early as 1908 with the introduction of posterior radicotomy by Foerster. Since then, numerous techniques for interrupting the spinal reflexes have been proposed, including longitudinal myelotomy, or stereotaxic operations such as cerebellar dentatectomy or thalamotomy[109]. Apart from a chemical or surgical partial peripheral neurotomy, which is a viable option when only a single muscle group is involved, only posterior root section continues to be employed. This is not the classical general root section involving all the posterior rootlets, but rahter a selective rootler section at the posterior spinal root junction[111]. The aim is selectively to destroy the small nocioceptive unmyelinated fibers, and converse the large myelinated fibers which carry non-nocioceptive somesthetic information. This technique is thought to be a value for spasticity of a limited distribution involving the territory of 2 or 3 roots at most. This is especially the case for those spastic syndromes of the arm arising in brachial diplegia secondary to cerebral palsy.

3.2.6 Conclusion

There is now enough evidence showing the superiority of lumbar intrathecal infusion of Baclofen to oral administration and even to destructive techniques for treating invalidating spasticity of spinal origin[71]. In theory at least, its remarkable efficiency obviated the need for double-blind trials. However, in a recent double-blind crossover study (Baclofen against saline), Penn *et al.*[97] provided additional evidence that intrathecal Baclofen markedly reduces severe spasticity. The advantages of the method are that it is conservative, non-invasive, reversible and selective in that it can suppress muscular hypertonus and inhibit mono and polysynaptic reflexes without affecting residual voluntary motor function. Bedridden or wheelchair patients with longstanding spastic paresis can also benefit from improved voluntary motor function. A difficulty is the marked inter-individual difference in response requiring accurate determination of individual effective doses. Continuous microperfusion gives better results than repeated bolus administration. The treatment of intractable spasticity by this new technique will rest on a firmer footing when we have a better understanding of Baclofen pharmacokinetics. The availability of specific antagonists and implantable programmable pumps with adequate sized reservoirs that are both reliable and inexpensive would also be highly desirable.

However, clinical trials with longer follow-up periods are still required to assess possible long-term tolerance. We also need to establish optimal efficient doses that suppress detrimental spasticity without interfering with residual voluntary motor function in ambulant patients.

4. Other Clinical Applications and Perspectives

4.1 Intracarotid and Direct Intratumoural Chemotherapy for Malignant Glioma

4.1.1 The Rationale

The overall effect of antimitotic agents depends on achieving adequate concentrations at the tumour site over a sufficient period of time. The brain and the cerebrospinal fluid are limited access sites, and drugs delivered systemically do not reach the central nervous system in high concentrations. The carotid artery is the principal afferent for the majority of the supratentorial gliomas. It would thus be a logical step to employ regional perfusion of anti-mitotic drugs[24, 35]. Injection of equal amounts of ^{14}C-labelled BCNU via the intravenous and intracarotid routes in monkeys showed that 3-fold higher concentrations were obtained in the ipsilateral brain with the intracarotid than with the intravenous route. In addition, the perfused cerebral hemisphere received 4 to 5-fold higher doses than the contralateral hemisphere.

The advantage of intravascular chemotherapy is that it localizes the cytotoxic agent, and avoids local increases in plasma peak concentrations. High local drug levels for prolonged periods, and diffuse distribution of the anti-mitotic throughout the tumour boundary have been achieved in the post-operative intra-cavity chemotherapy of malignant brain tumours via an external catheter[14, 39] or implantable pump[47, 79, 93].

4.1.2 Local or Regional Intracarotid Chemotherapy

The indications are essentially cerebral malignant glioma (III and IV grade astrocytoma) with a unilateral hemispheric situation and secondary diffuse metastases. Surgical extirpation and conventional radiotherapy are carried out prior to chemotherapy. Chemotherapy is either given systemically following radiotherapy, or if there is a recurrence. The results of intra-arterial chemotherapy using various chemical agents in these indications have been lesenbed by various authors[41, 42, 99]. Some of these preliminary studies are listed in Table 5. Most of the authors have employed the femoral approach for each session of chemotherapy (normally every 2–3 months). The aim is to increase selectivity (supra-ophthalmic), in order to reduce the risk of neurotoxic retinal effects. Prior to chemotherapy, the blood-brain barrier can be rendered permeable by intravenous or even intra-arterial infusion of hypertonic mannitol followed by a rapid infusion of BCNU or cisplatinum.

Implantable pumps have been employed only by a few workers in this indication. In [99]1982, Philips proposed a slow, continuous FudR perfusion

Table 5. *Regional Chemotherapy for Malignant Brain Tumours*

Authors	Patients		Technique		Site	Drug
	GL	M	Cath	P		
Greenberg *et al.* (1981) Greenberg (1984)	30		30		I-A	BCNU
Dakhil *et al.* (1981)	7			7	I-V	Metho-trexate
Philips *et al.* (1982)	6		6		I-A	BCNU, FUdR, Cisplatinum
Feun *et al.* (1984)	20	10	30		I-A	Cisplatinum
Stewart *et al.* (1984)	16	16	32		I-A	BCNU, Cisplatinum
Beck *et al.* (1984)		3		3	I-Th	Metho-trexate
Morantz (1984)	11			11	I-T	Bleomy-cin

GL = Gliomas grades III and IV; M = metastasis; Cath = femoral catheter; P = Pump; I-A = intra-arterial; IV = intraventricular; I-T = intratumoural; I-Th = intrathecal.

(4.8.–6.5 mg/day) using an Infusaid 400 model pump for a 14–70 day period. A side-port was used for repeated bolus injections of either BCNU or cisplatinum. Ocular toxicity is the major complication with this method[42], and it appears to be related to the alcohol concentration in the BCNU solution. Supra-ophthalmic catheterisation should thus reduce the risk of retinal toxicity. The second toxic risk is purely neurological and is independent of the route (intra or supra-ophthalmic) or method of infusion. Nevertheless, implantable, continuous-flow pumps allow simultaneous infusion of such "cell-cycle-specific" chemical agents as FudR or even radiosensitizers (BUdR). Another advantage of these slow continuous-flow pumps is their ability to maintain high tissue concentrations of drug. In the near future, connection of a slow-flow perfusion pump to an intra-arterial, supra-ophthalmic catheter should become feasible without compromising patient safety.

4.1.3 Direct Intra-tumoural Chemotherapy

Intra-ventricular chemotherapy has been reported[26], while direct implantation of a catheter at the tumour site has also been envisaged. Local administration of cisplatinum to rats has been reported by Kroin and

Penn[57], although it seems that tissue diffusion (maximum of 2 cm) limits such applications. Local chemotherapy is tempting as it would considerably reduce the neurotoxic and other risks inherent in the use of such powerful drugs. Local microinfusion may be the technique of the future. Bleomycin has been tested in cases of glioma[11, 79], and other drugs have been tried via multiple implanted catheters[14, 39, 93]. Recently, Harbaugh[47] reported a phase I study of intra-tumoural methotrexate infusion in recurrent glioblastoma. This author showed that post-operative intra-cavity methotrexate infusion through a single catheter as well tolerated if systemic folinic acid was given to prevent peripheral side effects. Radio-immuno assay demonstrated that drug diffusion and levels in the tumour (biopsy and autopsy samples) and surrounding brain tissue (biopsy samples) was much higher than those achieved by systemic administration. At the present time however data on efficacy are not available from this phase I study, and no significant tumour response has been observed so far. Conclusions will have to await the results of further studies with methotrexate and other chemotherapeutic agents.

4.2 Intraventricular Cholinergic Drug Infusion for Alzheimer's Disease

Progress in understanding the neurochemical deficits of various degenerative diseases of the CNS has led to the development of new applications for local infusion of drugs. Recent data indicate that there is a reduction in cholinergic cerebral acitivity in patients with Alzheimer's disease (A. D.). Cerebral biopsies of such patients were also found to have reduced amounts of choline acetyl transferase (ChAT), a specific marker of cholinergic neurones, as well as a decrease in acetylcholine synthesis[23, 28]. Based on the possibility of a decreased muscarinic receptor activity in A. D. patients, Harbaugh *et al.*[44] suggestd perfusing small doses of muscarine agonists directly into the ventricular cerebrospinal fluid.

After toxicity studies in dogs, 4 A. D. patients were subjected to a preliminary feasibility test followed by a cerebral biopsy. A constant flow pump (Infusaid) was connected to a catheter placed in the lateral ventricle in 3 patients and in the cisterna magna in the other. Bethanecol chloride was infused slowly until the optimal therapeutie dose for each patient was obtained (between 0.05 and 0.7 mg/day). During an 8 months follow-up period, he observed a number of spontaneous, reversible complications: initial nausea, and in one case, a transient Parkinsonian syndrome which regressed after reducing the dose (0.6 to 0.4 mg/day).Although the therapeutic response seemed encouraging, experience is still too limited for any general conclusions to be drawn. Subjective family reports noted improvement in cognitive function as well as in the patients' functional capacity. Patients returned to their initial state after infusion of a placebo. The

efficiency of this treatment has yet to be confirmed over a longer follow-up period with quantitative evaluation of mental function using standardized scales.

Since this initial study[44,45], Harbaugh[46] and Penn[95] have reported results of a double-blind study and escalating dose trials. They only noted moderate improvements in behavior and neuropsychological test scores after infusion of bethanecol, and they did not recommend treating this condition by infusion of any of the currently available drugs with implantable pumps. The prospects of this new therapeutic approach hinge essentially on neuropharmacological developments. In Alzheimer's disease for example, the goal is to find an agent that selectively reestablishes cholinergic activity. The possibility of supplying nerve growth factors directly to the brain of A. D. patients by intraventricular infusion has also been envisaged[50].

4.3 Intrathecal Infusion of TRH in Amyotrophic Lateral Sclerosis

The intrathecal administration of thyrotroping releasing hormone (TRH) in degenerative neurological diseases such as amyotrophic lateral sclerosis was proposed by Munsat[84]. It appears to be less toxic with a longer lasting effect by the intrathecal route than after intravenous administration. There is little information of date on the efficacy and the safety of this treatment, although a blind study is in progress[85].

4.4 Perspectives

There are many potential applications of direct CNS infusion of specific agents to treat neurological diseases or disorders. Systemic side effects, peripheral drug destruction, poor blood-brain barrier penetration often hamper drug therapy of such conditions[48, 70]. A number of trials can be mentioned:

Ballantine[6] has suggested that the intraventricular administration of lithium has potential psychiatric applications. Animal kinetic studies showed that intraventricular drug delivery can reduce both the extracerebral toxicity and the caudal neurotoxicity of lithium.

The intrathecal or intraventricular perfusion of anti-convulsant, glial 5-aminobutyric acid (GABA) uptake inhibitors such as THPO was suggested for the treatment of obstinate epilepsy[8, 48].

Intra-operative topical application of Nimodipine and post-operative intracisternal infusion of calcium inhibitors after repair of ruptured arterial aneurysms has been reported by Auer[4, 5]. Cisternal administration of Nimodipine (200 μg) was performed in 20 patients for 3 to 10 days postoperatively.

The use of L Dopa methylester in animal models of Parkinson's disease has been described by Hood[51].

Lastly, Harbaugh[48] has suggested the possibility of combining neural tissue transplantation with CNS infusion of neurotrophic factors.

Conclusion

Chronic intrathecal administration of opioids and Baclofen is now a routine therapeutic option for the control of pain and spasticity. The future prospects of local neuropharmacology are promising. They depend largely on progress in our understanding of the action of endogenous and exogenous ligands and the neurophysiological substrates of degenerative diseases. However, the neurotoxicity of new agents must be determined in rigorous animal toxicity studies before clinical trials.

From a technological standpoint, further developments in implantable and programmable drug delivery systems should be directed at improving reliability and safety, reducing cost and adapting the systems to patient needs. Over the coming generations, pharmacological neurosurgery is sure to see considerable development, and it represents a most promising field of research.

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